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Febrile seizures following measles and varicella vaccines in young children in Australia

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ABSTRACT

Background: Febrile seizures (FS) are common in childhood with incidence peaking in the second year of life when measles and varicella-containing vaccines are administered. This study aimed to examine the vaccine-attributable risk of FS following separate administration of MMR and monovalent varicella vaccines (VV) prior to a planned change to MMRV as the second dose of measles-containing vaccine at 18 months of age.

Methods: All FS cases in children aged <5 years from 1st January 2012 to 30th April 2013 were identified from emergency department (ED) and inpatient databases at five Australian tertiary paediatric hospitals participating in PAEDS (Paediatric Active Enhanced Disease Surveillance). Immunization records were obtained from the Australian Childhood Immunization Register (ACIR). The relative incidence (RI) of FS following MMR dose 1 (MMR1) and VV in children aged 11–23 months was determined using the self-controlled case series (SCCS) method and used to calculate attributable risk.

Results: There were 2013 FS episodes in 1761 children. The peak age at FS was 18 months. The risk of FS was significantly increased 5–12 days post receipt of MMR1 at 12 months (RI = 1.9 [95% CI: 1.3–2.9]), but not after VV at 18 months (RI = 0.6 [95% CI: 0.3–1.2]. The estimated excess annual number of FS post MMR1 was 24 per 100,000 vaccinated children aged 11–23 months (95% CI = 7–49 cases per 100,000) or 1 per 4167 doses.

Conclusions: Our study detected the expected increased FS risk post MMR1 vaccine at 12 months, but monovalent varicella vaccine at age 18 months was not associated with increased risk of FS. This provides baseline data to assess the risk of FS post MMRV, introduced in Australia as the second dose of measles-containing vaccine at 18 months of age in July 2013.

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1. Introduction

Febrile seizures (FS) are dramatic but common acute neurologic events with a cumulative all-cause incidence of up to 5% by age 5 years [1]. Most FS are due to viral infections, but when attributed to recent vaccine receipt, can cause both parent and provider confidence in the safety of vaccines to be impacted [1]. For more than a decade, a significant but low risk of FS in the 5–12 days post dose 1 of the measles–mumps–rubella (MMR) vaccine [2–5] and in the first 48-hours following whole cell pertussis containing vaccines [1,5] has been recognized. More recently, studies have identified a risk of FS after seasonal influenza vaccine [6,7], 13-valent pneumococcal conjugate vaccine [7] and the new combination measles–mumps–rubella–varicella (MMRV) vaccine [8–11]. In Australia, the 2010 temporary suspension of seasonal influenza vaccination use in children <5 years following an unexpected excess of febrile seizures from one influenza vaccine brand (Fluvax, bioCSL, Parkville, VIC, Australia) has heightened concern of FS as a potential adverse event following immunization [6].

In Australia MMRV vaccine given at 18 months of age replaced the second dose of MMR at 4 years and monovalent varicella vaccine at 18 months on the National Immunization Program (NIP) in July 1st 2013. MMRV was scheduled as the second dose of measles-containing vaccine at 18 months of age for two main reasons; (1) the early evidence of a 2-fold increased risk of FS following MMRV as the first dose of a measles-containing vaccine compared to MMR and varicella vaccine administered separately [8,10]; and (2) data from clinical studies showing no increase in fever incidence when MMRV was given as the second dose of measles-containing vaccine in the second year of life [12,13]. To assess the risk of FS before and after this schedule change, sentinel surveillance for FS is being conducted at multiple paediatric hospital sites in the Paediatric Active Enhanced Disease Surveillance (PAEDS) network [14]. The aims of this study were; (1) to describe the epidemiology, relative incidence and vaccine attributable risk of FS following MMR (dose 1 and 2) and VV (only dose) given separately prior to MMRV introduction and; (2) to assess the capacity of the sentinel surveillance network to detect FS risk post inclusion of MMRV on the NIP.

2. Methods

2.1. Case ascertainment

FS cases were ascertained retrospectively from 1st January 2012 to 30th April 2013 from the 5 PAEDS hospital sentinel sites across Australia: The Children's Hospital at Westmead Sydney (CHW), Royal Children's Hospital Brisbane (RCHQ), Royal Children's Hospital Melbourne (RCHV), Princess Margaret Hospital for Children Perth (PMH) and Women's and Children's Hospital Adelaide (WCH) as described elsewhere [14,15]. Together these hospitals contributed 137,744 paediatric hospitalisations (34% of approximately 400,000 annual paediatric hospital separations, excluding births, of children younger than 15 year old in the Australian population of 22.6 million [birth cohort = 309,582 in 2012]). Ethics approval was obtained in each hospital to conduct this surveillance.

Emergency department (ED) and inpatient databases at PAEDS sites were reviewed for presentations (admitted to hospital and non-admitted) coded as FS (Australian Modification of the 10th revision of the International Classification of Diseases [ICD-10-AM] code R56.0) for children aged 0 to 5 years. Date of birth, sex, and date of first and any subsequent FS presentations were obtained. Immunization status for all FS cases was obtained from the Australian Childhood Immunization Register (ACIR). During the study period vaccines used were Priorix, GSK and MMRII, bioCSL/Merck and Co (MMR), and Varilrix, GSK and Varivax, bioCSL/Merck and Co (VV).

2.2. Self-controlled case series analysis

The relative incidence (RI) of FS following receipt of MMR1 or VV was determined using the self-controlled case series (SCCS) method [16]. This is a case only method that compares the FS rates during times when a person is exposed to a 'risk' to rates during times when the same person is unexposed using a conditional Poisson regression model. This analysis was restricted to children aged 11 to 23 months during the study period as this was the age period during which maximal exposure to the vaccines of interest occurred. The SCCS analysis included children with a first occurrence of FS, or only included repeat FS episodes for the same child where the subsequent FS was separated by at least 7 days from a prior ED visit and/or hospitalisation for FS. This was undertaken to exclude multiple repeat FS which could have resulted from the same trigger (such as fever from vaccine virus replication). From previous studies, the increased risk of FS is known to occur approximately 5–12 days post MMR1, at the peak of vaccine–virus replication [2–4]. Therefore our main outcome measure was the risk of a FS in the 5–12 days post MMR1 or VV compared with the background rate. For both vaccines we also included a risk period of 13–30 days post vaccination and of 1–13 days prior to vaccination to account for the 'healthy vaccinee effect' (lower risk). The period of 13–30 days was of particular interest for VV due to potentially later onset and longer duration of adverse effects related to vaccine virus replication. We estimated that with approximately 850 cases, of whom 95% were vaccinated, we would have 80% power to exclude a RI for FS of 2 or more within the 7 day risk period of 5–12 days post vaccination, with an alpha level of 0.05 [17].

The primary analysis included the first FS within the age and date range of the study and controlled for age using 1 month age groups. A range of sensitivity analyses were also undertaken, including: (a) controlling for age using broader age groups [11–14, 15–18, and 19–23 months, respectively]; (b) including repeat FS episodes (episodes separated by at least 7 days); and (c) for VV only we also restricted the analysis to children with their first FS between 17–23 months (to avoid the large number of children aged 11–17 months not exposed to VV but vaccinated with MMR).

2.3. Calculation of number of vaccine-attributable cases and risk of FS after MMR1

The excess number of FS associated with MMR1 vaccination in children aged 11 to 23 months (N_1) and the attributable risk (AR) per 100,000 vaccinated children were calculated using the following formulas:

$$N_1 = ((\mathrm{RI} \times N_0) - N_0) \times \mathrm{PV}$$

$$\mathrm{AR} = \left(\frac{N_1}{(\text{population} \times \mathrm{PV})}\right) \times 100,000$$

The RI was obtained from the results of the primary SCCS analysis and PV (the proportion of the population aged 11 to 23 months vaccinated with MMR1) was estimated using ACIR vaccination coverage data for the national cohort of the same age. N_0 is the baseline number of FS cases expected in the 8 day risk period (days 5–12 post vaccination). N_0 was estimated using the number of ED presentations (admitted and non-admitted patients) at hospitals in the Sydney Metropolitan area with a diagnostic code for FS (either ICD-10 AM code R56.1 or the Systematised Nomenclature of Medicine—Clinical Terms [SNOMED] code 41497008) for children aged 11 to 23 months in 2012, obtained from the NSW Emergency